POSTER SESSION

# 1098 Markers of Risk in Stable Angina Pectoris

Monday, March 31, 2003, Noon-2:00 p.m.
McCormick Place, Hall A
Presentation Hour: Noon-1:00 p.m.

## 1098-89 The Neurohumoral Response to Exercise in Coronary Heart Disease and the Relationship With Inducible Ischemia

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**Background** Neurohumoral substances, in particular BNP, are increasingly recognised as important prognostic indicators in a wide spectrum of conditions involving heart failure. Neurohumoral testing is proposed as a potential adjunct to investigation of patients with coronary disease. Our aim was to investigate the response of ANP, BNP, NT BNP and cardiotrophin (CT-1) to stress and define the response in relation to ischaemia and inducible ventricular dysfunction in patients with angina. **Methods** 70 patients with stable angina and preserved ventricular function (angina group), and 32 healthy volunteers (controls) participated. All subjects had resting echocardiography to exclude systolic dysfunction or other significant pathology. 49 of the angina group also had stress echocardiography to determine the extent and severity of inducible ischaemia. Baseline bloods for ANP, BNP, NT BNP and cardiotrophin were taken under standardised conditions after 30 minutes resting. Subjects then underwent symptom limited exercise testing ( Bruce protocol) with bloods drawn at peak exercise and again at 15 and 30 minutes post exercise. Stress echocardiography was performed in the conventional manner with dobutamine infusion increasing in increments, and the addition of atropine if necessary, to achieve target heart rate. **Results** Baseline BNP and NT-BNP were significantly higher in patients with angina vs controls. ANP and BNP, but not NT-BNP or CT, rose on exercise, with rapid return to baseline levels, in both the angina group and the controls. This rise was exaggerated in BNP in the angina group. ΔBNP was significantly greater in the angina group vs controls. Quantification of the increase in BNP did not correlate with other indices of inducible ischaemia. **Conclusions** BNP and NT-BNP are elevated in angina with preserved ventricular function. BNP increases in an exaggerated manner during exercise stress in patients with angina. These findings warrant further investigation to determine the cause, and clinical implications of BNP release during exercise stress.

## 1098-90 Proinflammatory Cytokines and Neutrophil Activation in Stable Angina

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**Background**: There is evidence for a chronic immune activation in coronary artery disease (CAD), but the nature of this immune response is not fully defined. We examined the cytokine profile in patients with stable angina (SA) and related it to lymphocyte receptor expression and neutrophil activation. **Methods**: 45 men (< 60 years old) with SA and angiographically verified CAD were included as well as 45 healthy controls. Interleukin(IL)-6, IL-10, IL-4 receptor(R), IL-1 receptor antagonist(Ra) and C-reactive protein (CRP) were measured in serum. Three colour flow cytometry was performed on whole blood or purified neutrophils using monoclonal antibodies against CD3, CD4, CD8, CD19, CD11b, CD41a, CD62L, CD89, CD45, CD56, CD16. **Results**: Patients had higher levels of CRP, IL-6, IL-1Ra and IL-4R (see Table) and an increased IL-6/IL-4R ratio compared with controls (0,07 *vs* 0,04, p<0,001). They also had increased numbers of neutrophil-platelet complexes (CD41a+CD11b+CD45+). CRP ( $r$ = 0,6, p < 0,001) as well as IL-6, IL-1Ra and IL-4R were related to neutrophil-platelet complexes in patients but not in controls. CRP and cytokines were not related to lymphocyte receptor expression. **Conclusion**: Raised levels of CRP and a proinflammatory cytokine profile in SA patients were strongly associated with neutrophil activation, assessed by increased neutrophil-platelet adhesion. Our data indicate that neutrophil-platelet interaction is a dominant factor in the systemic inflammatory state of stable CAD.

| | Patients | Controls | p< |
|---|---|---|---|
| CRP mg/l | 4,1±5,8 | 1,3±1,1 | 0,01 |
| IL-6 pg/ml | 4,1±3,8 | 1,8±0,9 | 0,001 |
| IL-1 Ra pg/ml | 501±207 | 363±193 | 0,01 |
| IL-4R pg/ml | 55,6±13 | 48,2±9,5 | 0,01 |
| IL-10 pg/ml | 2,8±2,5 | 2,1±2,1 | NS |
| CD41a+CD11b+CD45+ cells/mm$^3$ | 541±334 | 376±174 | 0,01 |

## 1098-91 The Additional Value of C-Reactive Protein in Patients With Intermediate Coronary Lesions and a Normal Fractional Flow Reserve

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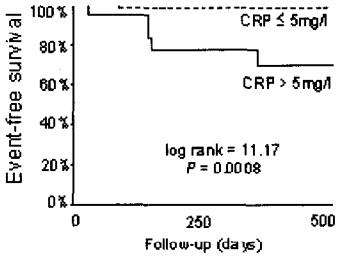
**Background:** Five to ten percent of patients still experience major adverse cardiac events (MACE) after deferral of PTCA based on a normal fractional flow reserve (FFR ≥0.75). This study was conducted to investigate the prognostic value of plasma C-reactive protein (CRP) in patients in whom PTCA was deferred based on a normal FFR.
**Methods:** Plasma levels of CRP were measured in 71 patients with stable angina undergoing cardiac catheterization for an intermediate coronary lesion with a mean diameter stenosis of 52%. Maximum hyperemia was induced by 20-40 µg IC adenosine to determine FFR, defined as the ratio of mean distal coronary pressure to mean aortic pressure during maximum hyperemia. Patients were followed for one-year for documentation of MACE related to the intermediate lesion. Receiver-operating-characteristic-curve analysis was used to evaluate the prognostic performance of CRP and to determine the best-cut-off-value (BCV).
**Results:** During follow up six (8%) MACE (1 CABG and 5 PTCAs) occurred. The BCV for CRP was determined at 5.0 mg/l. All patients, except one, in whom MACE occurred, had a CRP >5.0 mg/l (Figure). CRP was significantly higher in the group with compared to the group without MACE (median; 5.5 mg/l, range; 4.7-42.4 vs. 2.1 mg/l, range; 0.20-16.9, $P$=0.0001).
**Conclusion:** A low CRP is strongly associated with an uncomplicated follow up in patients with hemodynamic non-significant coronary lesions. Plasma levels of CRP are relevant for risk stratification in intermediate coronary lesions.




## 1098-114 PAPP-A, ProMBP, and PAPP-A/ProMBP Ratio Are Related to the Extent of Angiographic Coronary Artery Disease in Stable Angina Patients

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**Background:** Pregnancy associated plasma protein A (PAPP-A) is a metalloproteinase that has been related to the culprit plaque in unstable syndromes. PAPP-A liberates insulin like growth factor (IGF) from its binding protein and promotes IGF local effects. ProMBP (PAPP-A endogenous inhibitor) inhibits this effect. We studied the relationship among PAPP-A, ProMBP and PAPPA/ProMBP ratio and coronary disease extent in stable angina patients.
**Methods:** We studied 94 male patients (62±10 years old) with stable angina who underwent diagnostic coronary angiography. Patients were divided into 3 groups: Group 0 (no coronary artery stenosis > 50%); I (single vessel disease) and II (multivessel disease). Levels of PAPP-A and Pro-MBP were measured with an ELISA assay employing monoclonal antibodies.
**Results**: There were no significant differences between groups regarding traditional risk factors and medical treatments. Patients in group II were significantly older. PAPP-A levels and PAPP-A/ProMBP ratio were significantly higher and ProMBP levels significantly lower, in patients with greater coronary disease extent (table). After adjustment for risk factors, medications and age (multivariate linear regression) ProMBP and the ratio PAPP-A/ProMBP remained significant, although PAPP-A level was affected by the age.
**Conclusion:** PAPP-A/ProMBP ratio increases with the extent of disease, supporting the role of IGF in coronary disease and defines a better marker for coronary disease extent than PAPP-A itself.

| Oneway-ANOVA | Group 0 (n=25) | Group I (n=26) | Group II (n=43) | P value |
|---|---|---|---|---|
| Age | 58.4±10.3 | 58.7±11.2 | 66.3±8.7 | 0.001 |
| PAPP-A (mIU/L) | 5.1±1.4 | 5.0±1.0 | 6.0±1.9 | 0.017 |
| Pro-MBP (mIU/L) | 1892.8±391.0 | 1544.3±474.5 | 1585.7±647.9 | 0.042 |
| PAPPA/ProMBP | $2.8\pm0.6 \times 10^{-3}$ | $3.5\pm1.0 \times 10^{-3}$ | $4.2\pm1.5 \times 10^{-3}$ | <0.001 |